

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
1 February 2001 (01.02.2001)

PCT

(10) International Publication Number
WO 01/07410 A1(51) International Patent Classification⁷: C07D 213/50

(21) International Application Number: PCT/EP00/06825

(22) International Filing Date: 17 July 2000 (17.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

99114667.1 27 July 1999 (27.07.1999) EP
60/186,680 3 March 2000 (03.03.2000) US(71) Applicants (*for all designated States except US*): LONZA AG [CH/CH]; Münchensteinerstrasse 38, CH-4052 Basel (CH). MERCK & CO., INC. [US/US]; 126 Lincoln Avenue, Rahway, NJ 07065-0907 (US).

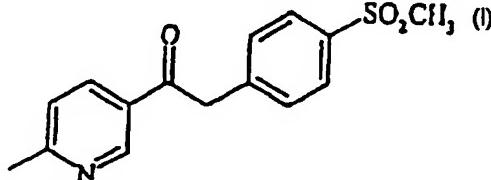
(72) Inventors; and

(75) Inventors/Applicants (*for US only*):—BESSARD, Yves [CH/CH]; Av. Rothorn 14, CH-3960 Sierre (CH). LERESCHE, James, Edward [CH/CH]; Kleegärtnerstrasse 25, CH-3930 Visp (CH).

(74) Agents: RITTHALER, Wolfgang et al.; Winter Brandl Fürniss Hübner Röss Kaiser Pothe, Alois-Steinecker-Str. 22, D-85354 Freising (DE).

(81) Designated States (*national*): AB, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TI, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).**Published:**— *With international search report.**For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: PROCESS FOR PREPARING 1-(6-METHYL PYRIDIN-3-YL)-2-[(4-(METHYL SULPHONYL) PHENYL] ETHANONE



(57) Abstract: A five-step process for preparing 1-(6-methylpyridin-3-yl)-2-[(4-methylsulphonyl)phenyl]ethanone of formula (I) described; characterized in that a) 4-(methylthio) benzyl alcohol is converted with hydrochloric acid into 4-(methylthio) benzyl chloride, b) 4-(methylthio) benzyl chloride is converted with an alkali metal cyanide into 4-(methylthio) phenylacetonitrile, c) 4-(methylthio)phenylacetonitrile is condensed with a 6-methylnicotinic ester to give 3-[2-(4-methylthio) phenyl]-2-cyanoacetyl] (6-methyl)-pyridine, d) 3-[2-(4-methylthio) phenyl]-2-cyanoacetyl] (6-methyl)-pyridine is hydrolysed and decarboxylated under acidic conditions to give 3-[2-(4-methylthio) phenyl] acetyl] (6-methyl) pyridine and, e) 3-[2(4-methylthio) phenyl] acetyl] (6-methyl) pyridine is oxidized to give the end product. The compound of formula (I) is an intermediate for preparing COX-2 inhibitors, pharmaceutically active compounds having analgesic and antiinflammatory action.

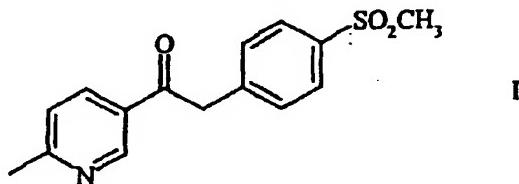
(57) Abstract: A five-step process for preparing 1-(6-methylpyridin-3-yl)-2-[(4-methylsulphonyl)phenyl]ethanone of formula (I) described; characterized in that a) 4-(methylthio) benzyl alcohol is converted with hydrochloric acid into 4-(methylthio) benzyl chloride, b) 4-(methylthio) benzyl chloride is converted with an alkali metal cyanide into 4-(methylthio) phenylacetonitrile, c) 4-(methylthio)phenylacetonitrile is condensed with a 6-methylnicotinic ester to give 3-[2-(4-methylthio) phenyl]-2-cyanoacetyl] (6-methyl)-pyridine, d) 3-[2-(4-methylthio) phenyl]-2-cyanoacetyl] (6-methyl)-pyridine is hydrolysed and decarboxylated under acidic conditions to give 3-[2-(4-methylthio) phenyl] acetyl] (6-methyl) pyridine and, e) 3-[2(4-methylthio) phenyl] acetyl] (6-methyl) pyridine is oxidized to give the end product. The compound of formula (I) is an intermediate for preparing COX-2 inhibitors, pharmaceutically active compounds having analgesic and antiinflammatory action.

Process for preparing 1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone

Description

5

The invention encompasses a novel process for preparing 1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone of the formula



10

1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone is an important intermediate for preparing so-called COX-2 inhibitors, pharmaceutically active compounds having analgesic and antiinflammatory action (R.S. Friesen et al., Bioorganic & Medicinal Chemistry Letters 8 (1998) 2777-2782; WO 98/03484).

15 The object of the invention was to provide a technically feasible process for preparing the intermediate of the formula I.

This object was achieved by the novel process according to Claim 1.

25

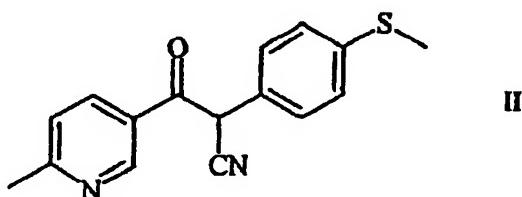
The process according to the invention is characterized by five steps, where,

30 in the first step a), 4-(methylthio)benzyl alcohol is converted with hydrochloric acid into 4-(methylthio)benzyl chloride,

- 2 -

in the second step b), 4-(methylthio)benzyl chloride is converted with an alkali metal cyanide into 4-(methylthio)phenylacetonitrile,

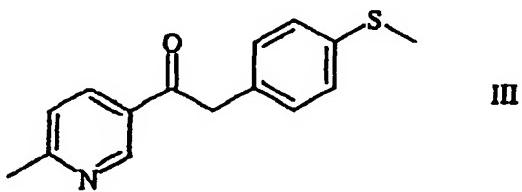
- 5 in the third step c), 4-(methylthio)phenylacetonitrile is condensed with a 6-methylnicotinic ester to give 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)-pyridine of the formula



10

in the fourth step d), 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine is hydrolysed and decarboxylated under acidic conditions to give 3-[2-(4-

- 15 (methylthio)phenyl)acetyl](6-methyl)pyridine of the formula



- 20 and, in the last step e), 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine is oxidized to give the end product.

Step a:

25

The chlorination of 4-(methylthio)benzyl alcohol to 4-(methylthio)benzyl chloride is carried out using hydrochloric acid, advantageously using concentrated hydrochloric acid, at a temperature of 30 from 10°C to 40°C.

- 3 -

The reaction is usually carried out in an organic solvent, advantageously in a water-immiscible solvent, such as, for example, in toluene.

5. Typically, the chlorination takes about 1 h to 4 h. The 4-(methylthio)benzyl chloride can be obtained in a simple manner by neutralizing the organic phase and removing the solvent. Further purification can be achieved by distillation.

10

Step b:

- 15 The cyanidation of 4-(methylthio)benzyl chloride is carried out using an alkali metal cyanide, advantageously in the presence of a phase transfer catalyst.

Suitable alkali metal cyanides are sodium cyanide or potassium cyanide.

- 20 The phase transfer catalysts which can be chosen are known in the art. Suitable are tetraalkylammonium halides, such as, for example, tetra-n-butylammonium chloride or tetra-n-butylammonium bromide.

- 25 In general, the reaction is carried out in the presence of a water-immiscible solvent, such as, for example, toluene; if appropriate, water can be added.

The reaction temperature is advantageously from 60°C to 100°C.

- 30 After a reaction time of 1 h to 6 h, the product can be isolated in a simple manner from the organic phase by removing the solvent.

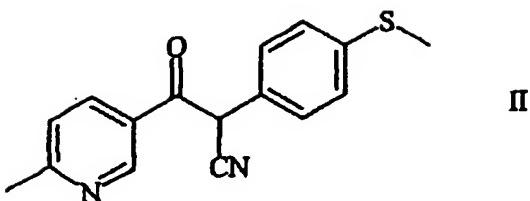
Further purification of the product can be achieved by recrystallization from, for example, diisopropyl ether.

Step c:

35

In the third step, ((methylthio)phenyl)acetonitrile is condensed with a 6-methylnicotinic ester to give 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl]-(6-methyl)pyridine of the formula

- 4 -



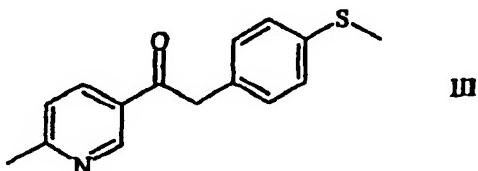
The condensation is advantageously carried out
5 in the presence of an alkali metal alkoxide, at a temperature between 60°C and 110°C.

Suitable alkali metal alkoxides are, for example, sodium methoxide or potassium tert-butoxide. The reaction is advantageously carried out in the presence
10 of a lower alcohol or an aromatic hydrocarbon as solvent.

After the condensation, the 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine can be obtained, for example, by adding the reaction mixture
15 to cold water and precipitating the product from the aqueous phase by acidifying it slightly.

Step d:

20 Hydrolysis and decarboxylation to give 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine of the formula



25

are carried out under acidic conditions.

Suitable acids are hydrochloric acid, phosphoric acid or mixtures of acetic acid with a mineral acid.

Advantageously, a mixture of acetic acid and a mineral
30 acid is employed, at a temperature of from 50°C to 115°C.

- 5 -

Particular preference is given to mixtures of acetic acid with concentrated hydrochloric acid or mixtures of acetic acid with concentrated sulphuric acid. If appropriate, a certain amount of water can be added to
5 the mixtures.

Good results were obtained using mixtures of acetic acid/concentrated hydrochloric acid 1:3 or acetic acid/concentrated sulphuric acid/water 1:1:1.

After a reaction time of about 1 h to 20 h, the mixture
10 can be neutralized using, for example, an aqueous ammonia solution, as a result of which the product precipitates out and can be isolated in a simple manner.

15 Step e:

Oxidation of 3-[2-(4-(methylthio)phenyl)-acetyl](6-methyl)pyridine to the end product is advantageously carried out using hydrogen peroxide in
20 the presence of an alkali metal tungstate, at a temperature of from 10°C to 40°C, preferably at about 20°C.

A particularly suitable alkali metal tungstate is sodium tungstate of the formula Na₂WO₄.2H₂O. The alkali metal tungstate is generally employed in catalytic amounts of from 0.5 mol% to 20 mol%, based on the 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine used.
25 The reaction is advantageously carried out in the presence of a lower alcohol as solvent. After a reaction time of about 1 h to 6 h, the end product can
30 be precipitated out by addition of water and then be isolated without any problems.

- 6 -

Examples

Preparation of 4-(methylthio)benzyl chloride

Under an atmosphere of nitrogen, 78.7 g (500 mmol) of 4-(methylthio)benzyl alcohol were dissolved in 154.5 g of toluene. 131.6 g, (1.3 mol) of conc. HCl were added, and the mixture was stirred at 20-25°C for 30 min. After 2 h (no starting material left according to TLC), the reaction mixture was diluted with 349 g of toluene and the aqueous phase was separated off. The organic phase was neutralized using 14.0 g of NaHCO₃ and, after 15 min, filtered, and the solvent was evaporated. The residue that remained consisted of 107.4 g of a yellow oil with toluene, corresponding to a yield of >95% (according to NMR).

¹H-NMR (CDCl₃): 7.30 (2H, d);
 7.22 (2H, d);
 4.55 (2H, s);
20 2.47 (3H, s).

¹H-NMR (DMSO): 7.37 (2H, d);
 7.25 (2H, d);
 4.73 (2H, d);
25 2.47 (3H, s).

Preparation of 4-(methylthio)phenylacetonitrile

Under an atmosphere of nitrogen, 25.9 g (150 mmol) of 4-(methylthio)benzyl chloride were dissolved in 45.5 g of toluene. 9.29 g (180 mmol) of sodium cyanide, 0.92 g (2.9 mmol) of tetrabutylammonium chloride and 14.4 g of water were then added. The mixture was stirred at 80-85°C for 2 h. The reaction mixture was admixed with 30 g of toluene and 45 g of water, the aqueous phase was decanted off and the organic phase was concentrated. This gave a residue of 24.6 g of the title product in a yield of >95% (according to NMR) in the form of a pink solid.

- 7 -

¹H-NMR (CDCl₃): 7.25 (4H, m);
 3.70 (2H, s);
 2.47 (3H, s).

5

Preparation of 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine

Under an atmosphere of nitrogen, a mixture of
10 38.5 g (250 mmol) of ethyl 6-methylnicotinate, 29.9 g
(500 mmol) of sodium methoxide (90.5%) and 300 ml of
toluene was added, at 85-90°C and over the course of
30 min, to a solution of 47.3 g (250 mmol) of
4-(methylthio)phenylacetonitrile in 75 ml of toluene.
15 This mixture was stirred under reflux for 14 h, then
distilled until the overhead temperature exceeded 110°C
and kept at reflux for another 6 h. The reaction
mixture was poured into 500 g of ice water, the organic
phase was decanted off and the aqueous phase was
20 extracted with 3 x 100 ml of toluene. The aqueous phase
was acidified to pH 6.0 using conc. HCl. The resulting
yellow-beige suspension was filtered and the residue
was washed with water and dried. This gave 53.9 g (76%)
of the title product in the form of a yellow solid.

25

¹H-NMR (CDCl₃): 9.00 (1H, s);
 8.10 (1H, d);
 7.3 (5H, m);
 5.45 (1H, s);
30 2.60 (3H, s);
 2.45 (3H, s).

Preparation of 3-[2-(4-(methylthio)phenyl)acetyl]-(6-methyl)pyridine

35 A mixture of 8.0 g (28 mmol) of 3-[2-(4-(methylthio)phenyl)-2-cyanoacetyl](6-methyl)pyridine,
20 ml of acetic acid and 60 ml of concentrated
hydrochloric acid was heated at 95°C to 100°C for
1.5 h.

- 8 -

The orange solution was cooled and adjusted to pH 10 using concentrated ammonia solution. The resulting yellow-beige suspension was filtered and the residue was washed with water and dried. This gave 5.35 g (74%)
5 of the title product in the form of a yellow solid.

¹ H-NMR (CDCl ₃):	9.10 (1H,s); 8.15 (1H,d); 7.2 (5H,m); 10 4.21 (2H,s); 2.61 (3H,s); 2.45 (3H,s).
--	--

Preparation of 1-(6-methylpyridin-3-yl)-2-[(4-(methyl-
15 sulphonyl)phenyl]ethanone

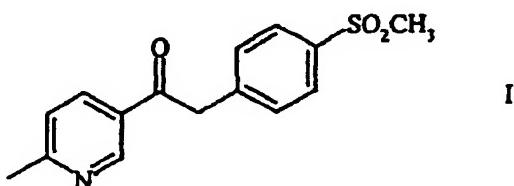
Under an atmosphere of nitrogen, a suspension of 8.9 g (34.5 mmol) of 3-[2-(4-(methylthio)phenyl)-acetyl](6-methyl)pyridine in 90 ml of methanol was heated to 55°C and adjusted to pH 4.5 using 2 N sulphuric acid. An aqueous solution of 0.22 g (0.7 mmol) of sodium tungstate in 7 ml of water was then added. At 55°C, 10 mol of hydrogen peroxide were then added over the course of 1 h, and the mixture was then cooled to room temperature and filtered. The 25 slightly beige filtration residue was washed using 2 × 30 ml of a mixture of water/isopropanol 2:1 and 2 × 30 ml of water and then dried under reduced pressure at room temperature. This gave 7.43 g of the title product in a yield of 75%.

¹ H-NMR (CDCl ₃):	9.15 (1H,s); 8.18 (1H,d); 7.92 (2H,d); 7.47 (2H,d); 35 7.30 (1H,d); 4.39 (2H,s); 3.04 (3H,s); 2.63 (3H,s).
--	---

- 9 -

Patent claims

- 5 1. Process for preparing 1-(6-methylpyridin-3-yl)-2-[(4-(methylsulphonyl)phenyl]ethanone of the formula



10

characterized in that
in the first step a), 4-(methylthio)benzyl alcohol
is converted with hydrochloric acid into
4-(methylthio)benzyl chloride,

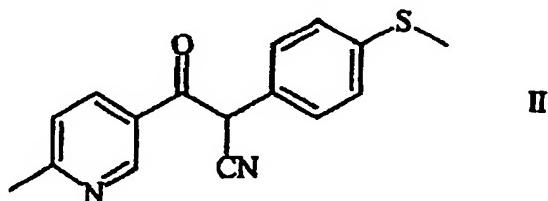
15

in the second step b), 4-(methylthio)benzyl
chloride is converted with an alkali metal cyanide
into 4-(methylthio)phenylacetonitrile,

in the third step c), 4-(methylthio)-
phenylacetonitrile is condensed with a

20

6-methylnicotinic ester to give 3-[2-(4-
(methylthio)phenyl)-2-cyanoacetyl](6-methyl)-
pyridine of the formula

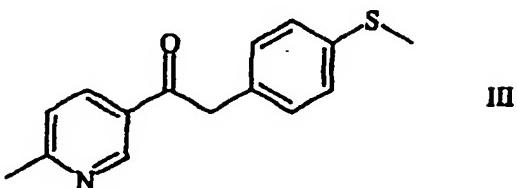


25

in the fourth step d), 3-[2-(4-
(methylthio)phenyl)-2-cyanoacetyl](6-methyl)-
pyridine is hydrolysed and decarboxylated under
acidic conditions to give 3-[2-(4-

- 10 -

(methylthio)phenyl)acetyl](6-methyl)pyridine of
the formula



5

and, in the last step e), 3-[2-(4-(methylthio)phenyl)acetyl](6-methyl)pyridine is oxidized to give the end product.

10 2. Process according to Patent Claim 1, characterized in that the reaction in step a) is carried out at a temperature of from 10°C to 40°C and in an organic solvent.

15 3. Process according to Patent Claim 1 or 2, characterized in that the reaction in step b) is carried out in the presence of a phase transfer catalyst.

20 4. Process according to any of Patent Claims 1 to 3, characterized in that the reaction in step b) is carried out at a temperature of from 60°C to 100°C.

25 5. Process according to any of Patent Claims 1 to 4, characterized in that the condensation in step c) is carried out in the presence of an alkali metal alkoxide at a temperature between 60°C and 110°C.

30 6. Process according to any of Patent Claims 1 to 5, characterized in that the hydrolysis and decarboxylation in step d) is carried out using a mixture of acetic acid and a mineral acid, at a temperature of from 50°C to 115°C.

- 11 -

7. Process according to any of Patent Claims 1 to 6,
characterized in that the oxidation in step e) is
carried out using hydrogen peroxide in the
presence of an alkali metal tungstate, at a
5 temperature of from 10°C to 40°C.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/06825

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BURGER A. & WALTER JR., C.R.: "Some .alpha.-substituted .beta.-pyridylethylamines" THE JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 72, no. 5, May 1950 (1950-05), pages 1988-1990, XP002128997 * compounds XII and XIII * page 1990, left-hand column	1-7
Y	US 3 717 647 A (VILLANI F.J.) 20 February 1973 (1973-02-20) column 10, line 1 - line 20 column 12, line 1 - line 15	1-7
Y	US 4 115 578 A (MILLER G.A. & OWEN R.P.) 19 September 1978 (1978-09-19) column 15; example 26	1-7
-/-		

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 September 2000	09/10/2000
Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hartrampf, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/06825

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 062 238 A (F. HOFFMANN - LA ROCHE & CO. AKTIENGESELLSCHAFT) 13 October 1982 (1982-10-13) page 6	1-7
Y	WO 99 15503 A (MERCK & CO., INC.) 1 April 1999 (1999-04-01) claims 1-13; examples 2-4	1-7
A	WO 98 47871 A (MERCK & CO., INC.) 29 October 1998 (1998-10-29) page 14 -page 16	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/06825

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 3717647	A	20-02-1973	NONE		
US 4115578	A	19-09-1978	AR 226407 A	15-07-1982	
			AR 220522 A	14-11-1980	
			AU 502679 B	02-08-1979	
			AU 1087376 A	11-08-1977	
			BR 7600736 A	31-08-1976	
			CA 1065323 A	30-10-1979	
			CH 619697 A	15-10-1980	
			CS 197264 B	30-04-1980	
			DD 124098 A	02-02-1977	
			DE 2604047 A	16-09-1976	
			DK 48076 A	06-08-1976	
			ES 444918 A	01-11-1977	
			ES 458202 A	16-08-1978	
			FR 2300081 A	03-09-1976	
			GB 1530172 A	25-10-1978	
			GR 58522 A	29-10-1977	
			HU 178950 B	28-07-1982	
			IE 43517 B	25-03-1981	
			IL 48975 A	31-03-1980	
			IT 1061007 B	20-10-1982	
			JP 51143667 A	10-12-1976	
			MX 4047 E	23-11-1981	
			NL 7601206 A	09-08-1976	
			NZ 179937 A	25-09-1978	
			OA 5234 A	28-02-1981	
			PT 64778 A, B	01-03-1976	
			SE 7600674 A	06-08-1976	
			TR 18878 A	13-10-1977	
			US 4118461 A	03-10-1978	
EP 62238	A	13-10-1982	AT 11537 T	15-02-1985	
			AU 547799 B	07-11-1985	
			AU 8213882 A	07-10-1982	
			DE 3262096 D	14-03-1985	
			ES 510913 D	16-04-1983	
			ES 8305357 A	01-07-1983	
			GR 75540 A	27-07-1984	
			HU 187668 B	28-02-1986	
			IL 65338 A	30-06-1985	
			PT 74674 A, B	01-04-1982	
			US 4380544 A	19-04-1983	
			JP 57175187 A	28-10-1982	
			ZA 8201968 A	26-01-1983	
WO 9915503	A	01-04-1999	AU 9500298 A	12-04-1999	
			EP 1023266 A	02-08-2000	
WO 9847871	A	29-10-1998	AU 7257198 A	13-11-1998	
			CN 1260782 T	19-07-2000	
			EP 0975596 A	02-02-2000	
			HR 980206 A	31-12-1998	
			PL 336298 A	19-06-2000	